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Citation	Journal Of Infection, 2004, v. 49 n. 4, p. 262-273
Issued Date	2004
URL	http://hdl.handle.net/10722/48634
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Medical treatment of viral pneumonia including SARS in immunocompetent adult

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Keywords: Viral pneumonia; Treatment; SARS; Immunocompetent host

Abstract

Since no randomized controlled trials have been conducted on the treatment of viral pneumonia by antivirals or immunomodulators in immunocompetent adults, a review of such anecdotal experience are needed for the more rational use of such agents. Case reports (single or case series) with details on their treatment and outcome in the English literature can be reviewed for pneumonia caused by human or avian influenza A virus (50 patients), varicella-zoster virus (120), adenovirus (29), hantavirus (100) and SARS coronavirus (841). Even with steroid therapy alone, the mortality rate appeared to be lower when compared with conservative treatment for pneumonia caused by human influenza virus (12.5% vs 42.1%) and hantavirus (13.3% vs 63.4%). Combination of an effective antiviral, acyclovir, with steroid in the treatment of varicella-zoster virus may be associated with a lower mortality than acyclovir alone (0% vs 10.3%). Combination of interferon alfacon-1 plus steroid, or lopinavir/ritonavir, ribavirin plus steroid were associated with a better outcome than ribavirin plus steroid (0% vs 2.3% vs 7.7% respectively). Combination of lopinavir/ritonavir plus ribavirin significantly reduced the virus load of SARS-CoV in nasopharyngeal, serum, stool and urine specimens taken between day 10 and 15 after symptom onset when compared with the historical control group treated with ribavirin. It appears that the combination of an effective antiviral and steroid was associated with a better outcome. Randomized therapeutic trial should be conducted to ascertain the relative usefulness of antiviral alone or in combination with steroid.

Introduction

The start of the new millennium is marked by two emerging infectious diseases coming from wild game food animals and poultry [1, 2]. Both SARS coronavirus (SARS-CoV) and avian influenza A H5N1 virus predominantly manifest as acute community acquired pneumonia with no response to empirical treatment by antibacterials covering typical and atypical agents [3-7]. SARS-CoV and avian influenza A H5N1 pneumonia are associated with significant mortality [7, 9]. Unfortunately, few prospective studies have been performed with documentation of the virus load changes during the course of illness for any respiratory viral pneumonia [8, 10]. The literature on the histological changes or pathogenesis of this condition is scarce. No randomized placebo-controlled treatment trial has ever been conducted. Such lack of data was often attributed to the lack of rapid diagnostic tests and effective antivirals. During the SARS outbreak, the empirical use of ribavirin and steroids were regarded as controversial [11-14]. Due to the explosive nature of the outbreak, randomized controlled trials on treatment could not be organized. Therefore, we attempt to review the literature on the rationale and strategy used in the treatment of acute community acquired viral pneumonia in immunocompetent adults. Virus load data and serological changes of acute respiratory viral pneumonia available in the literature, as well as from our SARS patients were included in this analysis.

Materials and methods

All the case reports and series with clinical details involving medical therapy of viral pneumonia including SARS in patients aged 15 years or above were included in this review. Patients with immunosuppressive conditions such as congenital or acquired immunodeficiencies, solid or marrow transplants, undergoing chemotherapy, and pregnancy were excluded. Where appropriate, the cited bibliographies were also retrieved for analysis.

Preliminary review of these publications suggested that viral pneumonia caused by SARS-CoV constituted the majority of cases reported in the literature. However, similar to other causes of viral pneumonia, little information on the virus load changes with respect to treatment was systematically reported. Therefore laboratory data from our cohort of 152 SARS patients who fulfilled the modified WHO definition were retrieved [5]. Virus load was measured on nasopharyngeal, serum, stool and urine specimens taken between day 10 and 15 after symptom onset. Part of these data was previously reported [8, 10, 15, 16]. The virus load results were correlated with the specific antiviral regimens, namely ribavirin with and without lopinavir/ritonavir for SARS. Serial quantitative RT-PCRs and IgG titers of SARS-CoV were performed in 12 randomly selected patients who were treated with ribavirin and corticosteroid on day 5, 10, 15 and 20 after onset of symptoms. To compare the serial virus load and antibody seroconversion with other respiratory virus infections, the English-language literature was searched to identify studies with detailed description of serial virus load and antibody titers during the course of infection.

Results

In the literature review, there were 1997 and 322 English publications on human studies identified in PubMed when the combination of keywords “virus, pneumonia, treatment” and “SARS, treatment” were used on 11 January 2004 respectively. Among the 1997 publications, those related to HIV and AIDS patients (950), cancer and transplant patients (501), and vaccine and immunization topics (287), were excluded. The remaining 259 papers were retrieved and analyzed. All the 322 SARS paper were retrieved and analyzed. Subsequent PubMed search using the keywords of “influenza, pneumonia, treatment”, “respiratory syncytial virus, pneumonia, treatment”, “varicella, pneumonia, treatment”, “adenovirus, pneumonia, treatment”, and “hantavirus pulmonary syndrome, treatment” identified another 623, 267, 240, 146, and 83 papers respectively. The cited bibliographies, if relevant, were also included in this review. However, only 62 of these 1940 papers contained clinical details and information on the medical treatment of viral pneumonia (44 papers) and SARS (18 papers) respectively.

Of the 302 patients with non-SARS viral pneumonia in 44 case reports or series (table 1), their etiological diagnoses of human influenza A (n=38), avian influenza A H5N1 (n=12), varicella-zoster virus (VZV) (n=120), adenovirus (n=29), hantavirus (n=100), respiratory syncytial virus (RSV) (n=1), measles (n=1), and Epstein-Barr virus (EBV) (n=1), were documented by a combination of clinical features, radiographic changes, virological and serological tests [6, 7, 17-58]. Demographic details were mentioned in 171 (56.6%) patients. There were 113 males and 58 females, with a median age of 31 years (ranged 15-88). The small number of patients suffering from pneumonia caused by RSV, measles,

EBV precluded any meaningful analysis or discussion [56-58]. As for the other agents, the overall mortality ranges from 9.2% (VZV), 20.7% (adenovirus), 31.6% (human influenza A), 49% (hantavirus) to 66.7% (avian influenza A H5N1).

In the treatment of human influenza A infection, antiviral agents such as rimantadine (1 patient), oseltamivir (5 patients), and a combination of rimantadine and oseltamivir had been used at a median of 3 days (ranged 1-7 days) after admission [20-23]. High dose corticosteroid without antiviral therapy was also attempted [20-22]. The dose of steroids ranged from hydrocortisone 250 mg ivi every 4 hours to methylprednisolone 500 mg ivi every 6 hours [21, 22]. Amantadine (4 patients), oseltamivir (3 patients), and a combination of antivirals and corticosteroid (3 patients) had also been used in the treatment of avian influenza A H5N1 [6, 7]. There was no apparent benefit since the antiviral agents were started at a median of 5 days (ranged 0-5 days) after admission. Corticosteroid such as intravenous methylprednisolone 1-2 mg/kg every 6 hourly for 3 to 4 days had been given in 3 mechanically ventilated patients but 2 of them died of acute respiratory distress syndrome [6, 7].

As for VZV pneumonia, antiviral therapy including intravenous acyclovir 10-15 mg/kg every 8 hourly for 7 to 10 days was initiated in 66 out of 120 patients [26-38]. Two patients were treated with vidarabine before the widespread use of acyclovir [27, 38]. Corticosteroids were combined with acyclovir in 17 patients [28, 29, 39-41]. The dosage and duration of steroids were quite variable (table 1) [29, 39-41]. Two patients received intravenous immunoglobulin (IVIG) together with intravenous acyclovir had a favorable

outcome [42, 43]. The mortality of patients who received acyclovir or vidarabine alone was 7 out of 68 (10.3%), whereas 4 patients managed with supportive care died. Only 1 out of 25 patients died if intravenous acyclovir was initiated within 4 days of admission [27, 34, 35]. There was no death in patients treated with a combination of acyclovir and immunomodulators such as corticosteroid and IVIG [28, 29, 39-43].

As for adenoviral pneumonia, no antiviral was ever used for their treatment. Two of 4 (50%) patient receiving steroid died, which appeared to be higher than patients managed conservatively [21, 44-50]. The mortality for hantavirus pulmonary syndrome treated with intravenous ribavirin (47.7%) appeared to be only slightly lower than those treated conservatively (63.4%) [51-55]. The use of methylprednisolone was associated with a dramatic decrease of mortality to 13.3% [52, 53].

Though there were 849 cases of SARS with treatment details reported in the literature, many of these patients were diagnosed according to the clinical criteria issued by WHO with or without laboratory confirmation (table 2) [3-5, 8, 10, 59-71]. One of the case series was not included because patients treated by different treatment regimens were aggregated together and could not be analyzed [72]. There were 349 males and 500 females. Except for 13 (1.5%) patients who were treated conservatively, antiviral therapy and / or immunomodulating therapy were given in all other patients. Of 772 patients receiving specific antiviral therapy and / or immunomodulating therapy, 675 (87.4%) were treated with ribavirin containing regimens and 44 (5.7%) were treated with lopinavir/ritonavir containing regimens during the initial phase of the disease.

Immunomodulating therapy without antiviral agents was initiated in 53 of 772 (6.9%) patients. Recombinant interferon alpha, corticosteroid, and a combination of interferon alfacon-1 and corticosteroid were used in 30 (3.9%), 14 (1.8%) and 9 (1.2%) cases respectively. Of the 64 patients receiving treatment during clinical deterioration, ribavirin or oseltamivir, lopinavir/ritonavir, and convalescent plasma were given as rescue medical therapy in 32 (50%), 31 (48.4%), and 1 (1.6%) respectively. High dose pulse methylprednisolone was used during clinical deterioration such as oxygen desaturation, worsening of radiographic infiltrates in the chest, recurrent fever without evidence of nosocomial sepsis in some reports. However, the number of patients requiring pulse steroids was not mentioned in most of them [5, 8, 10, 59-62]. Furthermore, intravenous immunoglobulin, thymic peptides, and recombinant human thymus proteins were used in some patients but the clinical details were not sufficient for any meaningful analysis [61]. The overall mortality was 7.7% in these 849 SARS cases. No obvious difference was noted irrespective of whether the patients were treated by ribavirin with or without corticosteroids, corticosteroids alone, or recombinant interferon-alpha given on admission or during deterioration. However, the mortality is only 2.3% in a group of 44 patients treated by lopinavir/ritonavir, ribavirin and corticosteroids [64], and 0% for 9 patients treated with interferon alfacon-1 and corticosteroids [65]. Only 1 patient received convalescent plasma as rescue therapy [67].

Of the 152 SARS patients in our cohort, their clinical presentation, virological tests results, and treatment regimens have been previously reported [8, 10, 16]. The virus load of their nasopharyngeal, serum, stool, and urine specimens collected between day 10 and

15 after onset of symptoms are tabulated in table 3. There was no significant relationship between virus load, age, and the presence of co-morbidities. However, significant decreases in virus load were observed when lopinavir/ritonavir was added to ribavirin (table 3). It is also interesting to note that stool virus load is significantly higher in males (7.0 vs 5.5 log₁₀ copies/ml, p=0.02), whereas that of the urine is significantly higher in females (1.6 vs 0.6 log₁₀ copies/ml, p=0.01). Of the 111 (73%) historical controls treated with ribavirin and corticosteroids, 12 randomly selected patients had serial virus load studies performed on their nasopharyngeal specimens; their mean virus loads were 5.2, 7.3, 4.9, and 3.8 log₁₀ copies/ml at day 5, 10, 15, and 20 after onset of symptoms respectively (figure 1). The decline in virus load in nasopharyngeal specimens coincided with the appearance of IgG antibody titers against SARS-CoV during the course of infection (figure 2). Since similar clinical studies of other respiratory viral pneumonias were not available in the literature except for a naturally occurring case of influenza [73], another 12 cases of experimental infection with RSV by artificial inoculation into healthy volunteers were adopted for comparison (figure 2) [74]. The virus load of influenza A and RSV peaked at day 2 and 3 respectively, whereas that of SARS-CoV occurred at day 10 after onset of symptoms (figure 1). As for the antibody response, baseline antibodies of influenza A and RSV were detectable in serum and nasal washings but antibodies against SARS-CoV were not present until day 10 after symptom onset.

Discussion

Despite exhaustive laboratory investigations, an etiological agent could be identified in only around half of the patients suffering from acute community acquired pneumonia [75]. In immunocompetent adults with community acquired pneumonia, pyogenic bacteria still constitute the majority of microbiologically documented agents in prospective studies [76, 77]. The lack of readily available rapid diagnostic tests for respiratory viral infections is one of the major reasons for the lack of reports on the natural history, pathogenesis, and treatment of viral pneumonia. Well-documented treatment regimens by randomized control trials are only available for HIV, HCV, HBV, HSV, VZV, CMV, and human influenza without pneumonia [78-93]. Moreover, in-vitro susceptibility of viruses may not correlate with clinical efficacy, as in the case of interferon-alpha used for the treatment of genital herpes [94]. No improvement in symptoms score or duration of genital lesions was found irrespective of whether systemic or topical interferon-alpha was used [95]. In the case of acute RSV bronchiolitis, the efficacy of aerosolized ribavirin was also questionable [96, 97].

Due to the lack of effective antiviral therapy for viral pneumonia, alternative strategies using immunomodulation were proposed as early as the 1970s [21]. This was not unexpected, since the cytotoxic T cell response may lead to immunopathological damage after an initial period of host damage mediated by virus induced cytolysis. The present literature review suggests that at least in the case of human influenza A and hantavirus pneumonia, steroid therapy alone may improve the outcome [20-22, 52, 53]. In the case of VZV pneumonia, the absence of mortality in cases treated with the addition of steroid

to an efficacious antiviral agent such as acyclovir seems to support such an approach [28, 29, 39-41]. Despite some decrease in mortality in patients (47.7% vs 63.4%), ribavirin is not considered as an effective antiviral for hantavirus [51-55]. However, the use of steroids during the phase of severe acute respiratory distress syndrome of hantavirus pulmonary syndrome may be associated with reduction in mortality (13.3% vs 63.4%) [52, 53]. As emphasized by a group reporting on a cluster of adenoviral pneumonia, the use of high dose steroids without an effective antiviral may actually increase mortality [47]. However the number of adenoviral pneumonia treated by steroids is too small to justify such a conclusion. Overall, the dosage and duration of steroid therapy for viral pneumonia were extremely heterogenous, future randomized clinical studies should be conducted to ascertain the dosage and duration of steroids associated with the least complication which includes secondary infection and avascular necrosis of bone.

Another difficulty in the management of viral pneumonia is the early peaking of the virus load which leaves a narrow window of opportunity for antiviral treatment [73, 74]. In both human influenza A and RSV, the virus loads peaked at around 2 to 3 days after symptom onset in natural and experimental infections of healthy adults (figure 1) [73, 74]. The early control of virus load in these two infections may be explained by the brisk antibody response, possibly due to previous antigenic exposure (figure 2) [73, 74]. A completely different picture emerges in the case of SARS. The virus load in SARS patients peaked at around day 10 with a very large area under the curve when compared with those of human influenza A and RSV (figure 1). The onset of antibody response was also delayed and started to appear at around day 10. The failure of innate immunity

and the relatively delayed onset of adaptive antibody response to control virus replication may be the explanations for the high mortality of this infection. Our previous studies showed that mortality is directly related to the virus load in nasopharyngeal specimens on admission and at day 10 [16, 98]. The mortality was also correlated with the number of RT-PCR positive specimens from different body sites including nasopharyngeal, serum, stool, or urine [98]. Therefore, an effective antiviral which could reduce the peak virus load and area under the curve is the key to the successful treatment of SARS and perhaps avian influenza A H5N1, since the general population has no immunological memory towards these two viruses.

Intravenous ribavirin was empirically used as a broad-spectrum antiviral agent at the beginning of the SARS epidemic in many countries [3-5, 8, 59-63, 66]. Ribavirin was selected as it has broad-spectrum antiviral activities possibly through the interference of cellular inosine monophosphate dehydrogenase [99]. It has been shown to be effective against mouse coronavirus in the setting of fulminant murine hepatitis [100]. Although the in-vitro antiviral activity of ribavirin is weak, it has an indirect immunomodulatory activity by decreasing the release of proinflammatory cytokines from macrophages of mice. It may also switch the immune response of mice from a T-helper-2 to a T-helper-1 response [100], which is beneficial for most intracellular infection. Subsequently in-vitro susceptibility testing suggests that antiviral effect could only be achieved at a very high concentration which is difficult to achieve clinically [101], despite the fact that ribavirin is known to be concentrated in some cell lines such as African green monkey kidney (Vero 76) and mouse 3T3 cells [102]. Moreover, the use of high dose regimens indicated

for the treatment of hemorrhagic fever was associated with significant hemolysis [12, 72]. Thus other options were diligently searched during the epidemic. Lopinavir/ritonavir was then used in addition to ribavirin because of a weak in-vitro antiviral activity on the prototype SARS-CoV [10]. The checkerboard assay demonstrated synergism between lopinavir and ribavirin at a low viral inoculum [10]. Other reports suggested that glycyrrhizin, interferon beta (Betaferon), interferon alpha n-1 (Wellferon), interferon alpha n-3 (Alferon), leucocytic interferon alpha, and baicalin may also have in-vitro activity [101, 103-105]. However, interferons were not considered by most clinicians during the epidemic because of their known proinflammatory activity, which may potentiate the inflammatory damage initiated by the viral infection, and the reported side effects of interstitial pneumonitis and bronchiolitis obliterans organizing pneumonia [106]. Subsequently pegylated recombinant interferon alpha 2b was shown to be effective as pre-exposure and perhaps very early post-exposure prophylaxis in cynomolgus macaques (*Macaca fascicularis*) experimentally infected with SARS-CoV [107]. Though different preparations of interferons appeared to be effective in-vitro, only recombinant interferon alpha and interferon alfacon-1 has been used in SARS patients [61, 65]. Moreover it is still early to say which interferon is likely to be effective in human trial because contradictory reports on the in-vitro susceptibility tests were reported for interferon beta 1a [101, 108] and interferon alpha 2b [101, 109].

This review has reviewed the anecdotal reports on the treatment of viral pneumonia. The findings may be biased since positive results are more likely to be reported. Steroids appeared to confer some benefit in patients with ARDS due to hantavirus, human

influenza and VZV. However, the early use of high dose steroids may be counterproductive in the absence of an effective antiviral agent. Randomized placebo controlled trials utilizing different regimens of antivirals with or without steroids should be considered for the treatment of SARS and other viral pneumonias in the future.

Acknowledgment:

We acknowledge research funding from the Vice-Chancellor SARS Research Fund, Suen Chi Sun Charitable Foundation SARS Research Fund, The University of Hong Kong. We are most grateful to Dr Rodney Lee for critical review of the manuscript.

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Table 1. Summary of literature reported cases in the medical management of viral pneumonia other than SARS in immunocompetent host

Antiviral therapies and / or immunomodulating agents with respect to different viral pathogens; sex & age (if mentioned)	Number of cases	Mechanical ventilation (%)	Mortality (%)	Reference
Human influenza A pneumonia – 8 M / 8 F; median age 65 years (23-80 years)	38	24 (63.2)	12 (31.6%)	17-23
Conservative treatment	19	12 (63.2%)	8 (42.1%)	17-20
Antiviral alone: Rimantadine (1), oseltamivir (5), combination of oseltamivir & rimantadine (5)	11	8 (72.7%)	3 (27.3%)	20-23
Corticosteroid alone: MP 500 mg ivi q6h (1); hydrocortisone 250 mg ivi q4h and tailing from day 6 to day 26 after admission (1)	8	4 (50%)	1 (12.5%)	20-22
Avian influenza A H5N1 pneumonia - 6 M / 6 F; median age of 24.5 years (16-60 years)	12	6 (50%)	8 (66.7%)	6,7,24,25
Conservative treatment	2	0 (0%)	1 (50%)	24
Antiviral alone: Amantadine (4), oseltamivir (3)	7	3 (42.9%)	5 (71.4%)	6,24,25
Antiviral & immunomodulators: Amantadine for 3 days & steroid in 1; oseltamivir for 5 days & MP 1-2 mg/kg ivi q6h for 3 and 4 days in 2 patients respectively	3	3 (100%)	2 (66.7%)	6,7
VZV pneumonia - 61 M / 28 F; median age of 31 years (22-88 years)	120	37 (30.8%)	11 (9.2%)	26-43
Conservative treatment	33	2 (6.1%)	4 (12.1%)	26-29
Antiviral alone: Intravenous acyclovir (66), vidarabine (2)	68	26 (38.2%)	7 (10.3%)	27-38
Antiviral & immunomodulators: Intravenous acyclovir & corticosteroid (17), intravenous acyclovir & IVIG (2) (hydrocortisone 200 mg ivi q6h for 2 days in 6; hydrocortisone 100 mg ivi q6h and tailing over 1 month in 1; P 60 mg po qd and tailing over 32 weeks in 1; MP 60 mg ivi q6h for 2 days in 1 patient)	19	9 (47.4%)	0 (0%)	28,29,39-43
Adenoviral pneumonia -7 M / 3 F; median age of 22 years (18-48 years)	29	12 (41.4%)	6 (20.7%)	21,44-50
Conservative treatment	25	10 (34.5%)	4 (16%)	44-48
Corticosteroid alone	4	2 (50%)	2 (50%)	21,44,49,50
Hantavirus pulmonary syndrome - 30 M / 11 F; median age of 33 years (15-63 years)	100	25/56 (44.6%)	49 (49%)	51-55
Conservative treatment	41	18/26 (69.2%)	26 (63.4%)	51-53
Antiviral alone: intravenous ribavirin	44	NM	21 (47.7%)	51,54,55*
Corticosteroid alone	15	7 (46.7%)	2 (13.3%)	52,53
RSV pneumonia - F / 64; aerosolized ribavirin 6 gm 22 hours daily for 5 days	1	1 (100%)	0	56
Measles pneumonia - F / 29; MP 1 gm ivi daily for 2 days and tailing dose thereafter; vitamin A 200,000U orally for 2 days	1	1 (100%)	0	57
EBV pneumonia - M / 30; P 100 mg po daily for 11 days then tailing gradually	1	1 (100%)	0	58

Note. EBV, Epstein-Barr virus; MP, methylprednisolone; NM, not mention; P, prednisolone; ivi, intravenously; IVIG, intravenous immunoglobulin; RSV, respiratory syncytial virus; VZV, varicella-zoster virus; * patients described in reference 55 were also reported in reference 54.

Table 2. Summary of literature reported cases in the medical management of SARS in adult

Antiviral therapies and / or immunomodulating agents, in addition to empirical broad spectrum antibiotics therapy	Number of cases	Sex (M:F)	Non-invasive ventilation (%)	Mechanical ventilation (%)	Pulse MP for clinical deterioration (%)	Mortality (%)	Reference
Conservative supportive treatment	13	7:6	0	4 (30.8%)	0	2 (15.4%)	3,5,59,60,68-71
Initial medical management (n=772)							
Ribavirin with or without oseltamivir	47	19:28	10 (21.3%)	6 (12.8%)	0	3 (6.4%)	3
Ribavirin & corticosteroid	611	263:348	4 (0.7%)	104 (17%)	54 / 95 (56.8%)	47 (7.7%)	4,5,8,59-63
Ribavirin & high dose pulse MP	17	7:10	0	1 (5.9%)	4 (23.5%)	1 (5.9%)	63
Lopinavir/ritonavir, ribavirin & corticosteroid	44	12:32	0	0	12 (27.3%)	1 (2.3%)	10*,64
Corticosteroid	14	3:11	0	3 (21.4%)	2 (14.3%)	1 (7.1%)	65,68
Interferon alfacon-1 & corticosteroid	9	3:6	0	1 (11.1%)	5 (55.6%)	0	65
Recombinant interferon alpha	30	11:19	8 (26.7%)	2 (6.7%)	0	2 (6.7%)	61
Rescue medical treatment (n=64)							
Ribavirin or oseltamivir	20	5:15	0	6 (30%)	0	3 (15%)	66
Ribavirin & corticosteroid	12	6:6	0	12 (100%)	NM	1 (8.3%)	5
Convalescent plasma	1	F	0	0	1 (100%)	0	67
Lopinavir/ritonavir	31	13:18	0	3 (9.7%)	31 (100%)	4 (12.9%)	64

Note. MP, methylprednisolone; SARS, severe acute respiratory syndrome; SARS-CoV, SARS associated coronavirus. * 12 patients reported in reference 10 were included in reference 64.

Table 3. Correlation of demographic data, treatment intervention, and quantitative RT-PCR of clinical specimens between day 10 and 15 in 152 patients with SARS

Demographic data & treatment intervention	Nasopharyngeal specimens (n = 152)	Serum (n = 53)	Stool (n = 94)	Urine (n = 111)
	Mean (SD) virus load (log ₁₀ copies / ml)	Mean (SD) virus load (log ₁₀ copies / ml)	Mean (SD) virus load (log ₁₀ copies / ml)	Mean (SD) virus load (log ₁₀ copies / ml)
Age				
Age equal or more than 60 years (n=20)	2.5 (3.0)	1.2 (1.3)	6.7 (3.4)	1.4 (2.3)
Age less than 60 years (n=132)	2.3 (3.1)	1.1 (1.5)	6.0 (3.0)	1.3 (2.1)
P value	0.83	0.96	0.46	0.84
Sex				
Male (n=58)	2.9 (3.3)	1.4 (1.4)	7.0 (2.6)	0.6 (1.6)
Female (n=94)	2.0 (2.9)	1.0 (1.4)	5.5 (3.2)	1.6 (2.3)
P value	0.11	0.44	0.02	0.01
Co-morbidity				
Presence of co-morbidity (n=28)	2.9 (3.3)	1.1 (1.7)	5.9 (3.4)	1.2 (2.1)
Absence of co-morbidity (n=124)	2.2 (3.0)	1.1 (1.4)	6.1 (3.0)	1.3 (2.1)
P value	0.31	0.89	0.78	0.79
Lopinavir/ritonavir therapy in addition to ribavirin				
Presence of lopinavir/ritonavir therapy (n=41)	1.3 (2.6)	0.4 (0.9)	4.3 (3.3)	0.5 (1.4)
Absence of lopinavir/ritonavir therapy (n=111)	2.8 (3.1)	1.4 (1.5)	6.9 (2.6)	1.7 (2.3)
P value	<0.01	0.04	<0.01	<0.01

Figure legend

Figure 1. Sequential quantitative measurements of viral shedding from upper respiratory tract during infections with influenza virus, respiratory syncytial virus (RSV), and SARS coronavirus (SARS-CoV). Influenza virus quantitation was performed on throat washings from a naturally occurring case of influenza in a 28-year-old male. Influenza A / Victoria H3N2 virus was isolated using cell cultures [73]. RSV quantitation was done on nasal washings from 12 subjects inoculated nasally with $10^{4.7}$ TCID₅₀ (50 median tissue culture infectious dose) RSV A2 challenge pool of virus, developed by the National Institute of Allergy and Infectious Diseases. RSV virus load was measured by quantitative RT-PCR using primers based on the nucleotide sequences from the F gene of RSV group A and B viruses [74]. SARS-CoV quantitation was performed on nasopharyngeal specimens from infected patients. SARS-CoV virus load of 12 patients are measured by quantitative RT-PCR of *Pol* gene from nasopharyngeal specimens.

Figure 2. Changing titers of serum antibody of influenza A, nasal IgA of RSV, and IgG of SARS-CoV after onset of symptoms. Serum antibody titer (HAI) of influenza A was determined using serial sera from a patient who was naturally infected with influenza A virus (same patient as shown in Figure 1). Mean RSV nasal IgA titers were obtained from nasal washings of 12 subjects who were inoculated with RSV (same group of patients as shown in Figure 1). Mean IgG titers of SARS-CoV were obtained using sera from 12 patients who were infected with SARS-CoV (same group of patients as shown in Figure 1).

Figure 1.

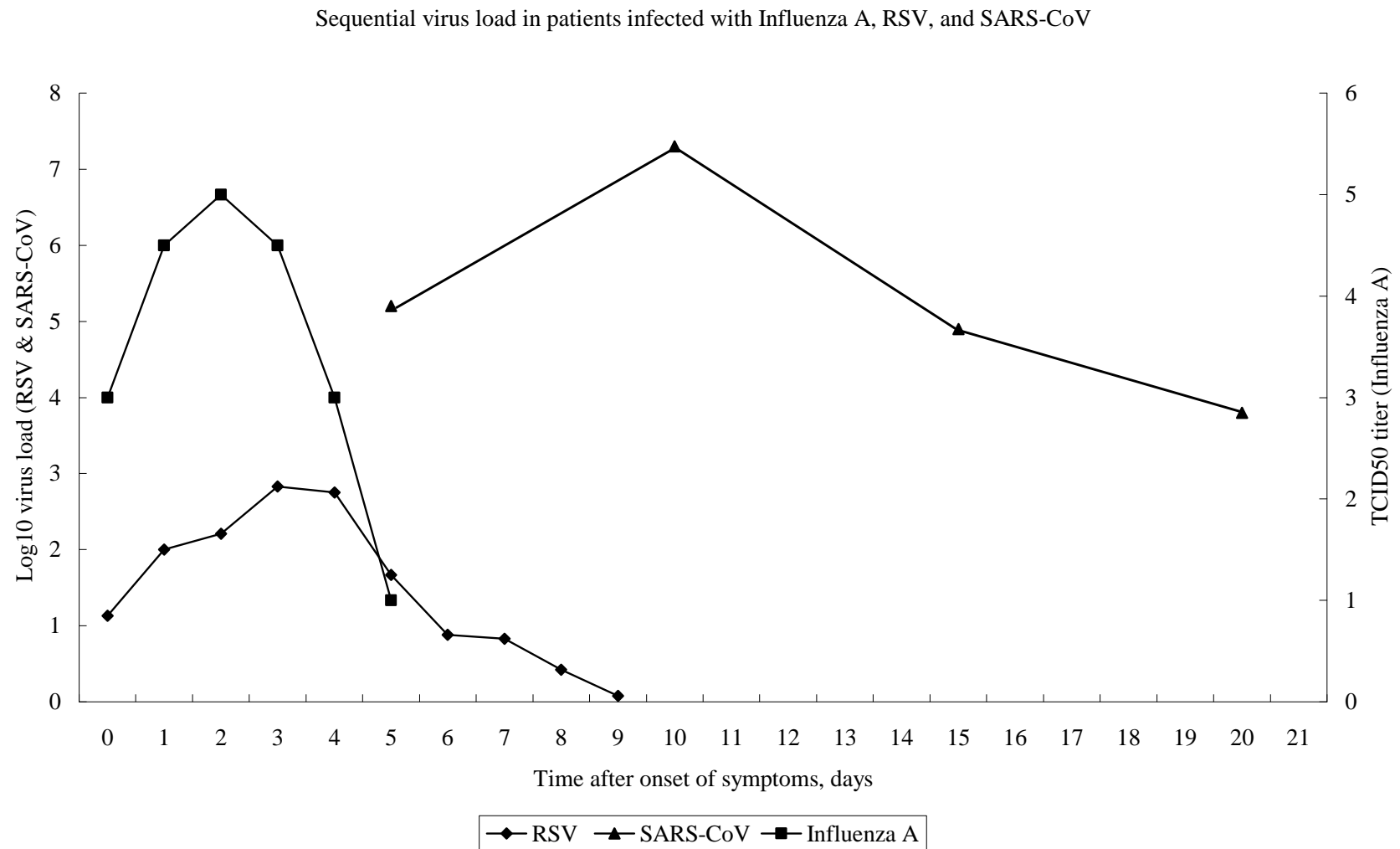


Figure 2.

